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THE OXO REACTION AS A SYNTHETIC METHOD*

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Shortly after the details of the German "Oxo Process" were revealed in the original patent by Roelen (1) and in reports by several investigating teams (2), Adkins and Krsek (3) reported on the application of this reaction, which they termed "hydroformylation," to several olefins, including those which contained various functional groups. These initial experiments indicated that the Oxo reaction was a potentially valuable synthetic tool for the preparation of aldehydes, including many which could be made only by difficult or lengthy alternate procedures. Despite this promise, the use of the Oxo reaction has rarely been reported outside of the patent literature and articles concerned with the mechanism of the reaction itself. No doubt, this reluctance to use the Oxo synthesis is based, to some extent, on the hazard of working with carbon monoxide under high pressures, but, if due care is exercised, hydroformylation is no more hazardous than high-pressure catalytic hydrogenation. However, the hydroformylation reaction has certain fundamental limitations which are of considerable importance when it is evaluated as a general method for synthesis of aldehydes.

Hydroformylation consists essentially in the addition of hydrogen and carbon monoxide to an olefinic linkage to produce an aldehyde. Thus, in the simplest case, hydroformylation of ethylene produces propionaldehyde.

$$CH_2{=}CH_2 + CO + H_2 \longrightarrow CH_3CH_2CHO$$

Hydroformylation of higher olefins presents certain complications. In the first place, the formyl group may add to either side of the double bond. Propylene, for instance, gives a mixture of butyraldehyde and isobutyraldehyde.

$$CH_3CH{=}CH_2 + CO + H_2 \begin{cases} \nearrow CH_3CH_2CH_2CHO \\ \searrow (CH_3)_2CHCHO \end{cases}$$

The relative amounts of isomers formed are determined primarily by steric factors. From propylene, butyraldehyde is formed in slight excess of isobutyraldehyde, the ratio being about 60/40. In the case of isobutylene, the product is practically all isovaleraldehyde.

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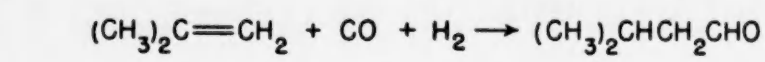
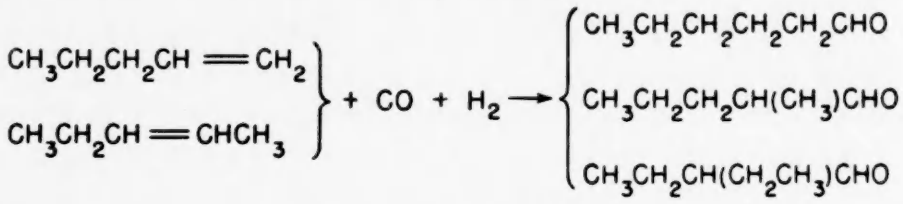
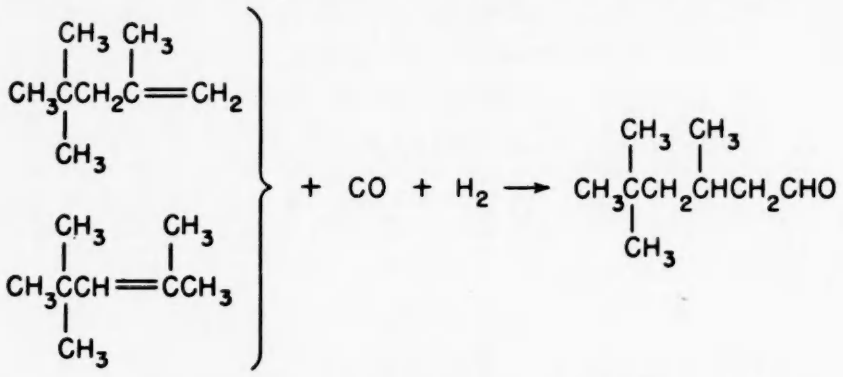


Some general rules have been formulated by Keulemans (4) to predict the formation of isomers: (a) Straight-chain olefins with a terminal double bond give 40-60% yields of primary carboxaldehydes and 60-40% yields of α-methyl carboxaldehydes; (b) a tertiary carbon atom is not formylated, that is, hydroformylation does not produce a quaternary carbon atom; (c) formylation of a carbon atom adjacent to a tertiary carbon atom is repressed, and no formylation takes place on a carbon atom next to a quaternary carbon atom; (d) formylation is not affected appreciably by isolated branching (branching on a carbon atom separated from the olefinic carbon atom by at least one intermediate carbon).

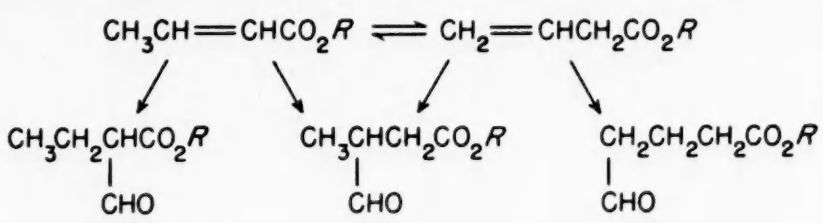
Another rule stated by Keulemans is very important: Isomerization of the double bond can occur prior to formylation. The relative amounts of aldehyde isomers are not governed by the thermodynamic stability of the olefins produced by this migration of the double bond but only by the steric factors just described. According to these rules, then, 1-pentene and 2-pentene should give the same mixture of C_6 aldehydes, and this has been confirmed by experiment (5).



Commercial diisobutylene is predominantly a mixture of two olefins of such structure that hydroformylation produces only one aldehyde.



The effect of polar substituents in the hydroformylation of olefinic compounds has not been studied thoroughly, and, unfortunately, erroneous reports of the structure of the products have been made in some cases. An interesting example is the hydroformylation of esters of crotonic acid. Adkins and Krsek, on the basis of studies by chromatography, reported that only one aldehydic ester was formed



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from ethyl crotonate and arbitrarily concluded that it was ethyl 3-methylsuccinaldehydate (II). Pino and co-workers (6) hydroformylated methyl and butyl crotonates and prepared a number of derivatives of the aldehydic esters, which they also characterized as 3-methylsuccinaldehydates. Since any α-formyl ester (I) would

probably condense to a resin, its absence in the distilled product was not considered proof that it was not formed in the Oxo reaction. This uncertainty was eliminated when Pino (7) ingeniously prepared the ester acetal in high yield by hydroformylation of ethyl crotonate in the presence of an orthoformic ester, and it was considered proof that the synthesis produced the β-formyl ester acetal exclusively. Hagemeyer and Hull (8), however, pointed out that a hydroformylation product of ethyl crotonate was ethyl glutaraldehydate (III). Migration of the double bond out of conjugation with the alkoxycarbonyl group would not be considered unusual in a highly branched unsaturated ester, but, for crotonate esters, this concept is surprising indeed. However, there is little doubt that migration does occur and that it is substantially complete, for all reports agree that essentially only one aldehydic ester is formed. Pino's data, incidentally, confirm Hagemeyer's and Hull's conclusion, for the physical constants of his derivatives agree with those reported for methyl glutaraldehydate (9), (10) and disagree with those reported for 3-methylsuccinaldehydic acid (11).

In view of this history, it is obvious that the Keulemans rules previously cited, especially the rule about double-bond migration, may be applicable to other olefinic compounds besides hydrocarbons, and that hydroformylation products should be characterized carefully. In a sense, the utility of the Oxo reaction has its exasperating side, for independent synthesis of the isomers that can be produced by a rapid one-step hydroformylation experiment can be very tedious.

Olefins with reactive functional groups bring more complications into the Oxo reaction. In the first place, the functional group frequently enhances the activity of the aldehyde formed, so that most of it condenses to useless resins. Any technique, such as high dilution or a low conversion of olefin, which produces a low concentration of aldehyde will help in this situation. In turn, the formyl group may activate the functional group of the original olefin. If hydroformylation of a chloroolefin produces a β-chloroaldehyde, the hydrogen chloride which is released effectively stops the hydroformylation reaction. In similar manner, the acetoxy group is lost from β-acetoxypropionaldehyde, one of the products of hydroformylation of vinyl acetate (12). Hydroformylation of allyl ethyl ether produces detectable amounts of methacrolein, presumably from partial decomposition of the β-ethoxyisobutyraldehyde (3).

A side reaction of variable importance in the Oxo reaction is simple hydrogenation of the double bond. Wender, Levine, and Orchin (13) showed that this reaction increases as the double-bond character of the olefinic bond decreases; that is, the more "aromatic" or conjugated the double bond, the more likely it is that hydrogenation rather than hydroformylation will take place. Thus, esters of crotonic acid are largely hydroformylated (although an appreciable amount of hydrogenation to butyrate esters occurs), but esters of cinnamic acid are only hydrogenated. Although only phenylpropionaldehydes were reported in the first work on hydroformylation of styrene (3), (14), Wender found that a 25% yield of ethylbenzene was formed in this reaction (13). In these Laboratories, attempted hydroformylation of propenylbenzene gave a 50% yield of propylbenzene. Adkins and Krsek noted that unsaturated aldehydes and ketones are hydrogenated under Oxo reaction conditions to the saturated carbonyl compounds. Wender and co-workers (16) made extensive studies on the hydrogenation of carbonyl compounds to alcohols, a reaction which takes place when hydroformylation conditions are applied at temperatures around 180°C.

Several attempts have been made to obtain dialdehydes by hydroformylation of

diolefins, but the products are the same aldehydes which would be expected to be formed from corresponding monoölefins (17). This is not surprising, since the initial hydroformylation of a diene would produce an unsaturated aldehyde, which would then be hydrogenated rather than hydroformylated. This would still be true for an unconjugated diolefin, if bond migration could occur, with formation of an α,β-unsaturated aldehyde. It is possible that the mechanism involves the preliminary reduction of the diene to an olefin (and presumably an unconjugated diene is first isomerized to the conjugated isomer), followed by hydroformylation. Peculiarly enough, diolefins which cannot form conjugate systems (for example, dicyclopentadiene) still give mostly monoaldehydes, although some success in preparation of dialdehydes has been reported (18). Dialdehydes can be prepared by hydroformylation of certain derivatives of unsaturated carbonyl compounds; for example, acrolein diacetate is hydroformylated to succinaldehyde-1,1-diacetate (3).

Elaborate equipment is not necessary to carry out Oxo reactions in the laboratory. The equipment normally used for high-pressure catalytic hydrogenations can be used for hydroformylations; however, a separate system is advisable, since equipment exposed to carbon monoxide is poisoned, at least temporarily, for hydrogenation service. Although it is decidedly more convenient to mix carbon monoxide and hydrogen in a 1:1 ratio and compress the mixture into the autoclave (or use a "synthesis gas" of approximately equal parts of carbon monoxide and hydrogen), the same effect is achieved by adding equal partial pressures of carbon monoxide and hydrogen from separate cylinders. Exact measurement is not necessary, but it should be noted that the reaction rate is increased by higher hydrogen pressures and decreased by excessive pressures of carbon monoxide (19). Pressures higher than cylinder pressure can be obtained by loading the autoclave at room temperature and then heating it to reaction temperature. This procedure limits the amount of gas to that of the original charge, and it is highly desirable that a small compression system be available for production of higher pressures.

Metallic cobalt catalysts, such as Raney cobalt, catalyze the hydroformylation reaction, but a more reproducibly active catalyst is preformed cobalt tetracarbonyl. This compound can be obtained by the action of carbon monoxide on certain cobalt salts (20) as well as on metallic cobalt catalysts (3). Cobalt carbonyl can be prepared and handled as a solution in an inert solvent, or the crystalline compound itself can be isolated. Cobalt tetracarbonyl is probably no less toxic than nickel carbonyl, but its low vapor pressure makes it decidedly less hazardous to handle.

Many hydroformylations can be run by charging catalyst, olefin, and solvent to the autoclave and treating the mixture with carbon monoxide and hydrogen at 100-200 atmospheres and 130-150°C. In many cases, however, superior results are obtained by adding the olefin gradually (by means of a small hydraulic pump) after the catalyst solution has been charged and brought up to reaction conditions. This technique helps in two ways: better control of the exothermic reaction is possible and the deleterious effect of excessive olefin concentration on the catalyst is avoided.

The manner of working up the hydroformylation mixture is quite important. Before any extensive fractionation is done, the reaction mixture should be distilled rapidly under reduced pressure to strip off the solvent. During this operation, volatile cobalt carbonyl derivatives may be distilled over. The rapid distillation is continued to obtain a crude distillate of the volatile hydroformylation product. This fraction may also be contaminated with cobalt carbonyl derivatives, but this is the exception rather than the rule. The crude distillate may now be fractionated with less danger of excessive condensation of the aldehydes, but prolonged heating

of a reactive aldehyde in the still pot will certainly reduce the yield. The yield of product obtained from a batchwise hydroformylation reaction will rarely exceed 60% and will frequently average only 30-50%. In many cases, however, yields of this magnitude are superior to the over-all yields of alternate multiple-step syntheses; in laboratory work, the time saved is well worth a sacrifice in yield.

References

1. Roelen, O., U. S. Pat. 2,327,066 (1943).
2. PB 81383, "The Oxo Process," Holm, M. M, and co-workers, February, 1947.
3. Adkins, H., and Krsek, G., *J. Am. Chem. Soc.*, *70,* 383-386 (1948); *Ibid.*, *71,* 3051-3055 (1949).
4. Keulemans, A. I. M., Kwantes, A., and van Bavel, T., *Reç. trav. chim.*, *67,* 298-308 (1948).
5. Naragon, E. A., Millendorf, A. J., and Larson, L. P., paper presented at the 117th Meeting of the American Chemical Society, Houston, Texas, 1950.
6. Pino, P., Mantica, E., and Paleari, C., *Ann. chim. (Rome)*, *40,* 237-250 (1950).
7. Pino, P., *Gazz. chim. ital.*, *81,* 625-634 (1951).
8. Hagemeyer, H. J., and Hull, D. C. (To Eastman Kodak Co.), U. S. Pat. 2,610,203 (1952).
9. Harris, S. A., Wolf, D. E., Mozingo, R., Arth, G. E., Anderson, C. R., Easton, N. R., and Folkes, K., *J. Am. Chem. Soc.*, *67,* 2096-2100 (1945).
10. McElvain, S. M., Degginger, E. R., and Behun, J. D., *Ibid.*, *76,* 5736-5739 (1954).
11. Owen, L. N., and Sultanbawa, M. U. S., *J. Chem. Soc. (London)*, pp. 3089-3098 (1949).
12. Gresham, W. F., and Brooks, R. E. (To E. I. du Pont de Nemours and Co. Inc.), U. S. Pat. 2,402,133 (1946).
13. Wender, I., Levine, R., and Orchin, M., *J. Am. Chem. Soc.*, *72,* 4375-4378 (1950).
14. Wetzel, L. A., McKeever, C. H., and Levesque, C. L., *Ibid.*, *72,* 4939-4940 (1950).
15. Unpublished work referred to by Orchin, M., in "Advances in Catalysis," Vol. 5, W. G. Frankenburg, E. K. Rideal, and V. I. Komarewsky, editors, Academic Press Inc., New York, N. Y., 1953, pp. 394-395.
16. *Ibid.*, pp. 387-391.
17. Adkins, H., and Williams, J. L. R., *J. Org. Chem.*, *17,* 980-987 (1952).
18. Büchner, K., Roelen, O., and Meis, J., Canadian Pat. 506,331 (1950).
19. Greenfield, H., Metlin, S., and Wender, I., paper presented at the 126th Meeting of the American Chemical Society, New York, N. Y., 1954.
20. Wender, I., Greenfield, H., and Orchin, M., *J. Am. Chem. Soc.*, *73,* 2656-2658 (1951).

New Eastman Organic Chemicals

P 2822	3-Benzoylacrylic Acid (Pract.) MP 91-94°	100 g.	$ 1.60
	$C_6H_5COCH{:}CHCOOH$ . . . MW 176.17	500 g.	6.05
7089	4,4′-Bis(4-amino-1-naphthylazo)-2,2′-stilbenedisulfonic Acid	1 g.	1.00
	$(NH_2C_{10}H_6N{:}NC_6H_3SO_3HCH{:})_2$ . . . MW 678.76	10 g.	5.50
	pH 8-9 (Indicator for pH)		
P 6959	Bis(α-methylbenzyl) Ether (Pract.) BP 146-150°/8 mm.	500 g.	1.90
	$[C_6H_5CH(CH_3)]_2O$ . . . MW 226.32	1 kg.	3.25
7082	*cis*-1,2-Dichloroethylene BP 59-60°	100 g.	1.50
	$CHCl{:}CHCl$ . . . MW 96.95	500 g.	5.60
1381	*trans*-1,2-Dichloroethylene BP 48-50°	100 g.	1.50
	$CHCl{:}CHCl$ . . . MW 96.95	500 g.	5.60
P 5927	(Ethylenedioxy)diacetic Acid (80%) (Pract.)	100 g.	1.65
	$(\text{-}CH_2OCH_2COOH)_2$ . . . MW 178.15	500 g.	6.15
P 1882	Ethylene Dibenzoate (Pract.) MP 71-73°	250 g.	1.65
	$C_6H_5COOCH_2CH_2OCOC_6H_5$ . . . MW 270.29	1 kg.	5.15
7031	Glycine Hydrochloride	100 g.	2.30
	$CH_2NH_2COOH{\cdot}HCl$ . . . MW 111.54	500 g.	9.50
7024	1,6-Hexanediamine Dihydrochloride	25 g.	1.60
	$NH_2(CH_2)_6NH_2{\cdot}2HCl$ . . . MW 189.14	100 g.	4.90
4025	1,6-Hexanediol MP 40-42°	25 g.	3.00
	$HO(CH_2)_6OH$ . . . MW 118.18	100 g.	10.50
7079	N-(2-Hydroxyethyl)-2-phenoxyacetamide MP 48-51°	25 g.	1.65
	$C_6H_5OCH_2CONHCH_2CH_2OH$ . . . MW 195.22	100 g.	5.00
P 7014	1-Octadecene (Pract.) MP 13-15°	100 g.	2.15
	$CH_2{:}CH(CH_2)_{15}CH_3$ . . . MW 252.49	250 g.	4.60
P 7080	Oxybis(2-ethylbenzoate) (Pract.) BP 225-227°/3 mm.	500 g.	1.80
	$C_6H_5COOCH_2CH_2OCH_2CH_2OCOC_6H_5$ . . . MW 314.34	1 kg.	3.10
P 7018	Sodium Dicyanamide (Pract.)	100 g.	1.40
	$NaN(CN)_2$ . . . MW 89.04	500 g.	5.10
7081	1,2,3,4-Tetrabromobutane MP 115-118°	100 g.	1.35
	$CH_2BrCHBrCHBrCH_2Br$ . . . MW 373.76	500 g.	4.75
4598	1,2,3,4-Tetrachlorobenzene MP 45-47°	500 g.	3.20
	$C_6H_2Cl_4$ . . . MW 215.91	1 kg.	5.85
7065	1,2,3,4-Tetrahydroisoquinoline BP 104-106°/8 mm.	10 g.	3.00
	$C_6H_4CH_2NHCH_2CH_2$ . . . MW 133.20	25 g.	6.75
T 2941	Thiophosphoryl Chloride (Tech.) BP 120-125°	500 g.	2.55
	$PSCl_3$ . . . MW 169.41	1 kg.	3.85

CORRECTION:

Listing of 3386 *p*-Ethoxy-N,N-diethylaniline should be
3386 *m*-Ethoxy-N,N-diethylaniline